DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION **Public Health Service**

Division or Cardio-Renal Drug Products **Memorandum**

Date : March 9, 2001
From : Director, Division of Cardio-Renal Drug Products, HFD-110
Subject : NonApproval of NDA 21-272, treprostinol (UT-15), Uniprost, United Therapeutics
To : Director, Office of Drug Evaluation and Review, HFD-100

Introduction

I support the conclusion that the results currently submitted to this NDA do not support approval of treprostinol for the treatment of pulmonary arterial hypertension. The attached reviews address the results and interpretation of the those results better than I can summarize. So, I will not try. This introduction summarizes some background that might be relevant to decision making. The body highlights some areas that caught my attention, but the detail in the reviews is critical.

Pulmonary Arterial Hypertension (PAH) is a hemodynamic abnormality characterized by mean pulmonary artery pressure greater than or equal to 25 mm Hg at rest (or greater than or equal to 30 mm Hg during exercise); pulmonary vascular resistance greater than 3 mm Hg/L/min, and mean pulmonary capillary wedge pressure less than or equal to 15 mm Hg. Many different diseases cause this hemodynamic abnormality. Among the etiologies of PAH is Primary Pulmonary Hypertension (PPH), which is a disease of unknown etiology, occurring mainly in women between the ages of 20 and 40 years. PPH is not a common disease.

Epoprostenol (prostacyclin, or PGI_2, Flolan) is an approved drug for the treatment of PPH. It has widespread use for the treatment of all forms of PAH. The data from NYHA class III and IV patients with PPH (open label, prospective, randomized trial) are generally taken to show an improvement of hemodynamics, exercise capacity, quality of life and survival, attributable to epoprostenol. It is administered into the great veins by back-pack infusion because of its irritant properties. Consequently, its use is reserved for highly symptomatic persons.

Treprostinol (UT-15) is an epoprostenol structural analog that can be kept chemically stable at neutral pH, and can be administered by subcutaneous infusion. This is a less burdensome means of administration. The pharmacology of treprostinol is like that of epoprostenol. Although treprostinol has 5 chiral centers, the stereospecific synthesis defines each chiral center and treprostinol is a single enantiomer.

In an exploratory trial (Study 01:03), involving 27 patients with PPH, treprostinol administered by continuous subcutaneous infusion for 6 weeks improved pulmonary hemodynamics and patients symptoms (details are in the medical review). This led to the design of 2 major controlled trials (P01:04 and P01:05) which involved patients with PAH, so the etiology of pulmonary hypertension was varied (but included PPH) in these 2 major trials. Among the reasons for the decision to study PAH (rather than PPH) was the current prevailing clinical perspective that PAH is the same hemodynamically regardless of etiology and that therapeutic responsiveness was independent of etiology, as well as having a more prevalent patient population to study.

A detailed statistical analysis plan was prospectively defined (before the trails P01:04 and P01:05 even began). In particular, the expectation was that a pooled analysis (of both trials together) would need to "only" yield a p of 0.01, provided that at least one of the trials rejected the null with a p of less than 0.05.

Major Results

Studies P01:04 and P01:05 were identical in basic design. They were randomized, double-blind, parallel-group, placebo-controlled, two armed trials. One group received placebo, the other received treprostinol, titrated to the highest tolerated dose (or to a maximum of 22.5 ng/kg/min). Each was 12 weeks in duration. Study P01:04 yielded 224 patients (113 receiving UT-15 and 111 receiving

placebo) and study P01:05 yielded 244 patients (119 receiving UT-15 and 125 receiving placebo) that were analyzed on an intent-to-treat basis.

The primary efficacy variable was the distance walked in 6-minutes. The range of walking distance (pooled studies) was 264.0 to 396.5 meters. The mean distance walked at baseline was 326.9 and 326.7 meters for the pooled studies, for the UT-15 group and the placebo group, respectively (page 17970 of the sponsor's Integrated Summary of Efficacy, 10/16/00). Over the course of 12 weeks (pooled analysis) the UT-15 treated group **decreased** their mean walking distance by about 2 meters and the placebo group **decreased** their mean walking distance by about 21 meters. Both groups had a decrease in the mean walking distance. The treatment effect was in the order of 19 meters (about a 7% less decrease in baseline walking distance, favoring treprpstinol). There are other numbers one can calculate, any way you cut that cake, the mean change is small, but one could not declare clinically meaningful.

As presented by the sponsor the results of the primary analysis. Expressed as median changes (page 17963 of the sponsor's Integrated Summary of Efficacy, 10/16/00) are in the following table. The FDA median change is not shown in the following table, but one result of p values for the same comparison is shown (there are others, less favorable).

Analysis Population Treatment Group	Sponsor Median Change (m)	Sponsor p-values	FDA p-values
Pooled 04/05			
UT-15 (N=232)	10.0	0.0064	0.015
Placebo ((N-236)	0.0		
Study P01:04			
UT-15 (N=113)	3.0[a]	0.0607	0.101
Placebo ((N-111)	1.0[a]		
Study P01:05			
UT-15 (N=119)	16.0[b]	0.0550	0.081
Placebo ((N-125)	-3.0[b]		

a) The treatment effect (Treated – Placebo) is 2 meters (Sponsor's analysis).
b) The treatment effect (Treated – Placebo) is 19 meters (Sponsor's analysis).

Here is where detail (there are many analyses) becomes very important and is beyond the purview of the memorandum. In short:

1) By the sponsor's primary analysis, they do not meet the "agreed to" criteria, namely a p of 0.01 for the pooled analysis, and a p of less than 0.05 for any single study.
    a) By FDA analyses, they fall even farther short of the predefined goal.

So what's the fuss? Well, irrespective of which analysis one is tempted to champion, nobody says that the trials found nothing, nor that UT-15 is clearly not a therapy for PAH. They found something, but is what they found sufficiently convincing to warrant approval?

It is not so clear that the change in walking distance detected in the trial was related to the baseline walking distance. According the sponsor's analysis (page 17998 of the sponsor's Integrated Summary of Efficacy, Table 8.7.7B) patients who could walk a mean distance of only 150 meters at baseline had a 51 meter treatment effect (a 34% mean **increase** in walking distance), whereas those that had a mean walking distance of 450 meters at baseline had a treatment effect of –2 meters (a 0.4% mean **decrease** in walking distance). A somewhat different perspective comes from FDA reviewer's analysis (page 120, Medical Review). This view does not deny the possible relationship between baseline walking distance and treatment effects. It does, however, put the relationship more in the form of hypothesis that needs confirmation in another study.

Similarly, the magnitude of the treatment effect detected in the studies appears dependent on NYHA class at the time of randomization. Those who were NHYA Class IV at randomization had a mean **increase** of 51 meters in walking distance, and those in NYHA Class II had a 2 meter **decrease**. Another hypothesis that requires confirmation.

The need to increase dose almost an order of magnitude during the course of the study is just a puzzle. The animal pharmacology, where one might think the question could be resolved, is not definitive with respect to the presence or absence of "tolerance". The human studies are consistent with tolerance, but are also not definitive.

This discussion could go on and on. Each part of each discussion is well laid out in the attached reviews. One can formulate many alternative of ways of looking at the data. All-in-all, although interesting, each fails to be convincing enough to warrant approval.

Mortality effects cannot be evaluated, only 19 total (9 patients receiving treprostinol, 10 patients receiving placebo). The number of hospitalizations totaled 78 (40 for patients receiving treprostinol and 38 for patients receiving placebo. There is little chance here to detect a signal that might function as guide to morbid/mortal effects.

This was a "feel good" development program. After appropriate study of 568 randomized patients, one can (perhaps) conclude that patients felt better, but if so, only barely detectably better. This (barely detectable) is not a strong argument for approval. Although treprostinol can be administered by subcutaneous infusion, a major not well understood (in relationship to dose) drawback is pain and irritation at the injection site, occurring in greater than 90% of the population treated with treprostinol. The pain is severe enough to require narcotic analgesics, in about 30% of the treated population. This is also not a pretty good argument for non-approval, since there is only a barely detectable gain.

Conclusion

I think that you should issue a non-approval letter, a draft of which is attached. Since the data are somewhat consistent with an effect different from placebo approval might be possible. Consequently, the attached draft package insert has been edited by the review team. It contains all of our suggestions, should you decide treprostinol is approvable.